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Trigeminal Nerve Stimulation Does Not Acutely Affect Cortical Excitability in Healthy Subjects

Hans W. Axelson, Mattias Isberg, Roland Flink, Åsa Amandusson*

Department of Clinical Neurophysiology, Uppsala University, Uppsala S-751 85, Sweden

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ABSTRACT

Background: Trigeminal nerve stimulation (TNS) has recently emerged as a new therapeutic option for patients with drug-resistant epilepsy but its potential mechanisms of action are not known. Since other antiepileptic treatments have been shown to alter cortical excitability, thereby reducing the liability to seizures, it has been suggested that cranial nerve stimulation such as TNS may act in the same way.
Objective: To study whether TNS has the potential to alter cortical excitability in healthy subjects.
Methods: An adaptive paired-pulse transcranial magnetic stimulation protocol stimulating the dominant hand motor area was used to measure resting motor threshold (rMT), short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI) before, during, and after 40 min of 120 Hz bilateral external continuous trigeminal nerve stimulation. Neuronavigation was used for guidance.
Results: TNS was well tolerated by all subjects. No significant changes were seen in the parameters studied.
Conclusion: Unlike for example anti-epileptic drugs and the ketogenic diet, trigeminal nerve stimulation does not seem to alter cortical excitability in healthy subjects. This is the first study on cortical excitability in relation to continuous trigeminal nerve stimulation. It still remains to be proven that TNS has the prerequisites to effectively counteract epileptic events in humans.

Introduction

The lack of efficient treatment alternatives to antiepileptic drugs and epilepsy surgery in patients with severe epilepsy has promoted the development of various types of neurostimulation such as repetitive transcranial magnetic stimulation, vagal nerve stimulation (VNS) and, more recently, trigeminal nerve stimulation (TNS). The rationale for using TNS as a potential treatment in epilepsy patients is largely based on its proposed antiepileptic effect in a rodent model where the amount and duration of pentylenetetrazole (PTZ)-induced seizures were clearly reduced by TNS [1]. The potential pathways of action of TNS are still unknown but have been suggested to be similar to those of VNS, considering that the trigeminal and vagal cranial nerves have in part similar projections in the central nervous system [2,3]. The afferent branches of the trigeminal nerve project extensively to the nucleus tractus solitarius (NTS) and locus ceruleus (LC) via the trigeminal nuclei. Both NTS and LC are known to be involved in the inhibition of seizures [4–6] and seem to be important to the therapeutic effects of VNS [7]. A suppression of neuronal firing in the primary somatosensory cortex in rats in response to trigeminal nerve stimulation has also been shown [8]. In a functional neuroimaging study in humans, many brain regions showed activation or deactivation in response to TNS [9]. There are thus multiple potential sites of action. It has been suggested that, regardless the pathways involved, the net result of peripheral/cranial nerve stimulation may be an altered cortical excitability [10–12]. The tendency to develop epileptic seizures is tightly linked to altered cortical excitability [13] and the cortical excitability has been shown to change in response to antiepileptic drugs (AED) [14–16], treatment with VNS [12], deep brain stimulation [17] and epilepsy surgery [18]. To our knowledge, no studies on the potential effects of trigeminal nerve stimulation on cortical excitability have been published so far.

Cortical excitability can be measured non-invasively in vivo using paired-pulse transcranial magnetic stimulation (ppTMS). In ppTMS, a subthreshold 'conditioning stimulus' (CS) to the motor cortex activates inhibitory and excitatory interneurons thereby conditioning the corticospinal output. A subsequent suprathreshold

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* Corresponding author. Tel.: +46 186113732.
E-mail address: asa.amandusson@akademiska.se (Å. Amandusson).

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'test pulse' (TS) may then elicit a reduced or increased motor response as compared to the unconditioned state depending on the interstimulus interval (ISI) [19–21]. In this study, we used a ppTMS protocol to measure cortical excitability in healthy subjects before, during and after trigeminal nerve stimulation.

Methods and materials

Subjects

20 healthy subjects were recruited (11 men and 9 women, age 31.9 ± 12.6 (mean ± SD), 18 right-handed and 2 left-handed). Exclusion criteria were a history of neurological or psychiatric disorder; a family history of seizure disorder; a history of seizures or unclear seizure-like episodes; facial pain; previous head trauma; pregnancy; pacemaker or other implanted stimulators; or metal objects in the head region. Two subjects were on oral contraceptives and one used antihistamines regularly. The study was approved by the regional ethical review board at Uppsala University (#2012/172) and written informed consent was obtained from all subjects.

Experimental setup

All sessions were carried out by the same operator and in the same room. The subjects were asked to remain seated in a comfortable chair with their eyes open throughout the session. To ensure relaxation of the limb muscles, the subjects were asked to keep their arms placed on a pillow and feet on a foot stand. Earplugs were used. All subjects were asked to fill in a questionnaire on side effects before and after the study. The study paradigm is depicted in Fig. 1.

Transcranial magnetic stimulation (TMS)

TMS was performed with two Magstim 200^2 units connected to a BiStim^2 module (the Magstim Company Ltd, Whitland, UK) using a figure-of-eight coil (Magstim 3190-00) with a loop diameter of 70 mm. Monophasic stimuli were given over the dominant hand motor cortex with the coil held tangential to the scalp at 45° to the anterior-posterior line with the handle pointing backwards. The BiStim^2 serial interface was used to control the intensity and timing of the stimuli via a laptop computer. The time interval between each single stimulus or pairs of stimuli exceeded 6 s throughout the study. A TMS navigation system (Visor2, ANT, Enchede, Netherlands) was used to keep the position and angle of the coil constant. A single subject 'standard MRI' was used in the navigation system to represent the brain surface and corrected in 3D to fit with the subject's fiducial markers.

MEP/EMG-recording

The registration of motor evoked potential (MEP) amplitudes was made from the first dorsal interosseus (FDI) muscle of the dominant hand using surface electrodes (Blue Sensor N, Ambu, Ballerup, Denmark). A 4.5 × 3 cm ground electrode (Neuroline, Ambu, Ballerup, Denmark) was placed on the dorsum of the hand. The compound muscle action potential (CMAP) peak-to-peak amplitude of the FDI was first obtained by supramaximal stimulation (Keypoint Workstation, Natus Medical Inc., San Carlos, USA) of the ulnar nerve 3 cm proximal to the distal wrist crease. If the CMAP amplitude was less than 10 mV, the recording electrodes were moved slightly to obtain a better recording position.

MEP peak-to-peak amplitude data were obtained using a PowerLab system (AD Instruments Ltd, Oxford, UK) and the signals were recorded at a sampling rate of 2 kHz. Filters were set to 20 Hz and 1000 Hz respectively. The sampling time range was −50 ms to 305 ms (with 0 ms as the time of discharge of the first TMS pulse). The free-running EMG was displayed continuously online throughout the sessions to ensure muscle relaxation during measurements. A custom-made computer application (Excel VBA, Microsoft, Redmond, USA) collected MEP amplitude data from the acquisition system and also controlled the BiStim^2 TMS parameters (see below).

Resting motor threshold (rMT)

The optimal position of the coil to elicit a MEP in the relaxed target hand muscle ('hotspot') in each subject was established using the TMS navigation system. The location of this hotspot was marked on the standard MRI and saved to the navigation system. All subsequent stimuli throughout the study were then given within ±1 mm distance from this point with a difference of the angle of the coil to the scalp of ≤5°.

The rMT was obtained by stimulating the hotspot using a 'best-PEST' (parameter estimation by sequential testing) procedure, a maximum-likelihood method in which a statistical approach is used to find threshold values [22–24], rMT was defined as the stimulus intensity (machine output, MO%) needed to obtain MEPs of 0.1 mV. 20 stimuli were given to establish this intensity according to the best-PEST algorithm.

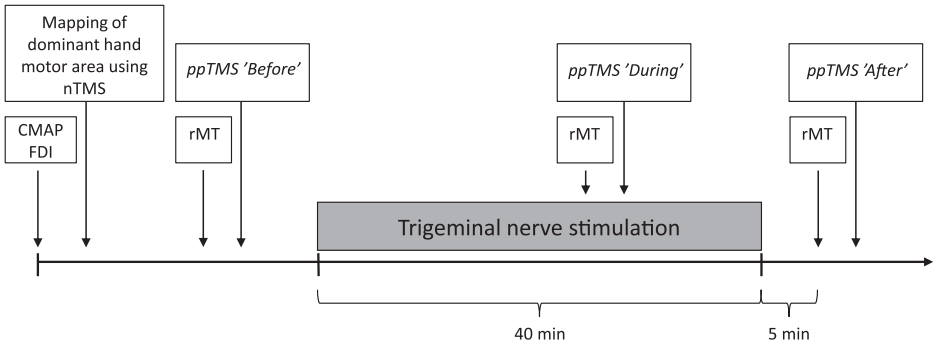

Figure 1. Experimental timeline. Following control measurement of the compound motor action potential (CMAP) of the first dorsal interosseus muscle (FDI), the cortical motor area of the dominant hand was mapped and the optimal position of the coil to elicit a motor evoked potential in the relaxed target hand muscle (FDI) was established using a TMS navigation system (nTMS). Subsequently, the resting motor threshold (rMT) was obtained followed by measurements of cortical excitability using paired-pulse transcranial magnetic stimulation (ppTMS) before starting the continuous trigeminal nerve stimulation (TNS) ('Before'). After 25 min of TNS, rMT and ppTMS-measurements ('During') were obtained during ongoing TNS. A third set of measurements of rMT and ppTMS ('After') was then performed 5 min after the TNS had been completed.

Paired-pulse TMS (ppTMS)

In conventional ppTMS, the CS and TS intensities are kept constant and changes in MEP amplitude are measured. Alternatively, it is possible to vary (adapt) the TS intensity so that, on average, the TS produces MEPs of predetermined amplitude after the conditioning stimulus. In the present study, the best-PEST method used for rMT estimation was also used for ppTMS. This adaptive ppTMS method is similar to the threshold-tracking technique previously described by Fisher 2002 and Vucic 2006 [25,26]. By using a constant target amplitude instead of constant stimulus intensity, it is possible to avoid the great variability of MEP amplitudes (up to 200% [27]) obtained by the conventional paired pulse technique, thereby potentially achieving more accurate ppTMS recordings [26]. Adaptive ppTMS may also be more sensitive in detecting differences in SICI as compared to the conventional method since it is not limited to a particular range of MEP amplitude reduction following the conditioning stimulus ('floor effect') [25,26,28,29]. The target amplitude for threshold-tracking in this study was chosen based on preliminary trials and set to 0.5 mV, which is within the range where the stimulus-response relationship is approximately linear on a log scale [25].

To measure potential changes in cortical excitability, ppTMS-measurements were undertaken at three time points: before, during and after trigeminal nerve stimulation (see below). A new rMT was obtained before each session. In total, 60 stimulation trials were carried out on each subject per session; 15 unconditioned MEPs (ucMEP) in addition to 15 conditioning-test pairs for each interstimulus interval (ISI) where ISI was set to 3, 13 and 150 ms. The three different intervals were chosen with the aim to produce short-interval intracortical inhibition (SICI) (3 ms), intracortical facilitation (ICF) (13 ms) and long-interval intracortical inhibition (LICI) (150 ms). Unconditioned control stimuli were alternated with the different paired stimuli in a randomized fashion. The CS was set to 80% of the rMT for SICI and ICF and 120% of the rMT for LICI. Paired-pulse TMS data were analyzed online using the custom-made software which also calculated the test stimulus intensities according to the best-PEST model. The final result obtained from the adaptive ppTMS measurements in each subject was thus estimates of the stimulus intensity needed to maintain the MEP amplitude at 0.5 mV with (SICI, ICF, LICI) or without (ucMEP) conditioning. Typically, excitability changes in response to a CS was demonstrated as an increase (SICI and LICI) or decrease (ICF) in the test stimulus intensity required to evoke the target MEP.

Trigeminal nerve stimulation (TNS)

Adhesive 4.5 cm × 3 cm disposable surface electrodes (same as the ground electrode) were applied on the forehead one cm above the supraorbital foramen bilaterally to stimulate the ophthalmic branch of the trigeminal nerve. The nerve was continuously stimulated with a biphasic pulse at 120 Hz and with 0.25 ms pulse duration using a Keypoint Workstation (Natus Medical Inc., San Carlos, USA). A separate oscilloscope unit (Lecroy, 9314M, Lecroy Corp., Chestnut Ridge, NY, USA) was used to confirm the integrity of the chosen stimulus pattern before the study was initiated. The stimulating current was gradually increased to obtain the highest stimulation strength possible without causing significant discomfort or muscle contraction. In a pilot study on 3 subjects (data not shown), it became evident that the subjects habituated to the stimulus very rapidly and the stimulation strength was therefore increased after 3 min of stimulation to the level where the current was again perceived but not painful. The mean stimulation strength was 4.4 mA (range 1.8–6.8, median 4.2 with all but one subject above 3 mA). The initial phase of titrating the right current strength took 5 min in total. The TNS was then maintained for 20 min before the second ('During') ppTMS session was started and was kept on during these measurements. In total, TNS lasted for 40 min. The last ppTMS session ('After') was performed 5 min after the TNS had been turned off.

Table 1
The results of cortical excitability measurements using the threshold-tracking ppTMS technique. The mean value, SD and range of the machine output (%) required to produce a motor evoked potential of 500 μV is shown for each occasion. $n = 20$. MT: motor threshold, SICI: short-interval intracortical inhibition, ICF: intracortical facilitation, LICI: long-interval intracortical inhibition.

	Before TNS			During TNS			After TNS		
	mean	*SD*	*range*	*mean*	*SD*	*range*	*mean*	*SD*	*range*
MT	42.7	6.6	30–57	42.7	7.0	29–56	42.6	7.2	28–59
ucMEP	47.0	9.9	30–72	46.2	8.1	31–62	46.6	9.7	29–69
SICI	59.0	17.4	30–100	57.2	16.2	31–92	57.7	15.6	27–86
ICF	45.1	7.4	29–63	44.4	7.3	30–57	44.6	7.4	30–60
LICI	54.2	12.1	29–84	53.7	12.0	30–80	54.4	12.9	28–86

Statistics

The excitability indices (SICI, ICF and LICI) were normalized [26] in relation to the ucMEP and expressed in percentage i.e., (conditioned test stimulus intensity − ucMEP)/ucMEP. Data were presented either as actual test stimulus intensities (Table 1) or as normalized values (Fig. 2). The Student's *t*-test was used for pairwise comparisons of the excitability measures between different time points in relation to trigeminal nerve stimulation (i.e., 'Before' vs. 'During,' 'Before' vs. 'After,' 'During' vs. 'After'). $P < 0.05$ was considered statistically significant. Statistical calculations were made using SPSS Statistics 19 (IBM, New York, USA). Unless otherwise stated, results are presented as mean ± standard error of the mean (SEM).

Results

The trigeminal nerve stimulation was well tolerated by all subjects. Most subjects described a tingling sensation on the forehead,

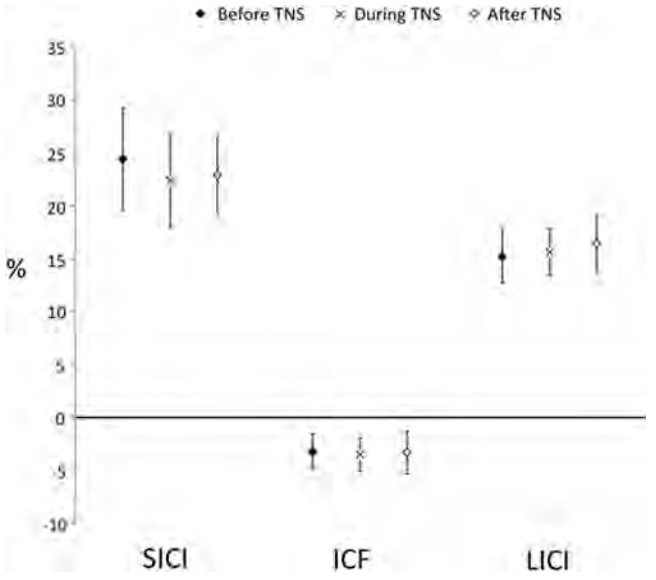

Figure 2. SICI (short-interval intracortical inhibition), ICF (intracortical facilitation) and LICI (long-interval intracortical inhibition) before (filled diamonds), during (x-markers) and after (empty diamonds) trigeminal nerve stimulation (TNS). The mean values are normalized to the ucMEP (see text for details). Vertical bars represent standard error of the mean.

one subject experienced a pressure sensation on the scalp and another subject reported a feeling of numbness behind the ears, all of which disappeared immediately after the stimulation was turned off. Two subjects experienced a slight headache from the TMS and one complained of numbness of the ulnar aspect of the right hand at the end of the session. The CMAP amplitude obtained from the FDI ranged from 12.3 to 28.8 mV with a mean of 20 mV.

Using the adaptive ppTMS technique described above, rMT and excitability measures (SICI, ICF, and LICI) were obtained (Table 1). There were no significant changes in rMT values between sessions. The rMT was thus stable throughout the experiment as was the stimulus intensity needed to elicit unconditioned MEPs (ucMEP), suggesting no significant changes in the integrity of the subject or testing environment during the experimental procedure. At baseline ('Before'), an inhibition (seen as a greater test stimulus intensity required to maintain the fixed MEP amplitude) was seen at ISI 3 ms (corresponding to SICI) and at ISI 150 ms (corresponding to LICI). A facilitation (seen as a decrease in stimulation strength needed) was seen at ISI 13 ms, corresponding to ICF (Table 1). The same pattern was seen in all sessions. None of the pair-wise comparisons over time ('Before' vs. 'During,' 'Before' vs. 'After,' 'During' vs. 'After') were significant in any of the measured values. The excitability measures related to the ucMEP (normalized data, see Statistics section above for details) at each time point are shown in Fig. 2. For SICI, the normalized value was 24.4 (±4.8) before TNS, 22.3 (±4.4) during TNS and 22.9 (±3.8) after TNS. The corresponding values for ICF were −3.2 (±1.6), −3.5 (±1.6) and −3.3 (±2.0) respectively and for LICI 15.2 (±2.5), 15.6 (±2.2) and 16.4 (±2.7). There were no significant excitability changes at any time point based on the data presented in Table 1 and Fig. 2 (*P*-values ranging from 0.20 to 0.96).

Discussion

The current study is the first to examine cortical excitability in relation to continuous trigeminal nerve stimulation (TNS). Given previous animal and human studies, there is a reasonable theoretical background for the assumption that TNS may have an antiepileptic effect, possibly by modulating cortical excitability, as mentioned in the Introduction. On the other hand, the recent phase II randomized controlled trial of TNS in patients with drug-resistant epilepsy showed no significant difference in effects between the active group and control group in any of the primary end points [30,31] and the trial was thus unsuccessful to prove the effectiveness of TNS in these patients. The present study failed to show any significant effects of TNS on excitability parameters in healthy subjects. Such effects have previously been shown in healthy subjects in response to other epilepsy treatments such as AED and ketogenic diet [32,33]. It thus remains to be proven that TNS has the prerequisites to effectively counteract epileptic events in humans.

The parameters of trigeminal nerve stimulation used in the present study were chosen in order to optimize the possibilities of inducing a cortical effect. We chose to deliver TNS by bilateral high-frequency stimulation since it seems to be more efficient according to previous studies [1,34]. This also closely mimics the parameters used by DeGiorgio et al. in their pilot trials on patients with epilepsy [3,35]. Whereas cyclic stimulation was used in those trials, we decided to use continuous stimulation based on the fact that several studies indicate that it is more efficacious than cyclic stimulation. For example, intermittent VNS was less effective than continuous VNS in animal studies [34] and continuous stimulation has been found to be potentially more efficacious than cyclic stimulation when it comes to other modes of neurostimulation such as deep brain stimulation in epileptic patients [17]. The stimulation strength was kept below pain threshold but above perception threshold in both studies but the resulting mean stimulation current intensity was lower in our study than in the pilot trials. In a recent pilot study on TNS in the treatment of major depression [36], in which a therapeutic effect was seen, a current intensity similar to ours was used.

This study was not placebo-controlled since the slight tingling sensation present during the active stimulation rules out the possibility of using a sham procedure. Instead, potential changes in excitability across time (before, during and after TNS) were analyzed. It should be noted, however, that we only measured the acute, not cumulative, effects of TNS. Evidently, the potential commercial device is aimed at longer treatment periods and a cumulative long-term effect has been shown in treatment with VNS [2,37,38]. It is possible that TNS has the ability to induce measurable changes in ppTMS parameters if given over a longer time period than in the current study. Still, a comparatively short stimulation time was enough to induce changes in cortical excitability in a study on VNS [11] and TNS has a very rapid antiepileptic effect in animals where automatic seizure-triggered TNS reduced PTZ-induced seizure activity [1].

It is important to note that the current study did not include patients with epilepsy. Epilepsy patients have an increased cortical excitability interictally when compared to healthy controls in many studies [14,39,40] and it remains to be seen whether TNS may affect ppTMS outcome in that group of patients.

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